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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,788	07/03/2003	George B. McDonald	8105-009-US-CON	6992

32301 7590 08/14/2008

CATALYST LAW GROUP, APC
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EXAMINER	
OLSON, ERIC	

ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
08/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/613,788	MCDONALD, GEORGE B.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
10613788	7/3/2003	MCDONALD, GEORGE B.	8105-009-US-CON

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EXAMINER	
Eric S. Olson	
ART UNIT	**PAPER**
1623	20080808

DATE MAILED:

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Commissioner for Patents

Detailed Action

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 29, 2008 has been entered.

This office action is a response to applicant's communication submitted May 29, 2008 wherein claims 1, 2, 7-13, and 16 are amended and claims 17 and 18 are cancelled. This application is a continuation of US application 09/753814, now abandoned, filed January 3, 2001, which claims benefit of provisional application 60/233194, filed September 15, 2000.

Claims 1-16 are pending in this application.

Claims 1-16 as amended are examined on the merits herein.

Applicant's amendment, submitted May 29, 2008, with respect to the rejection of instant claims 1, 2, 4, 5, 9, 10, and 18 under 35 USC 103(a) for being obvious over Punch et al. in view of Sequeria et al., has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to require that the topically active corticosteroid be beclomethasone dipropionate. Therefore the rejection is withdrawn.

The following rejections of record in the previous office action are maintained:

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10 and 12-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over McDonald et al. (Reference of record in previous office action) in view of Bertz et al. (Reference of record in previous office action)

McDonald et al. teaches that oral administration of the particular topically active corticosteroid, beclomethasone dipropionate (BDP), **alone** in the form of a capsule or **in combination with prednisone** (in the language of instant claim 16) is useful in a method of treating graft-versus-host disease in a human following organ allograft transplantation or stem cell transplantation for 30 days (see abstract and page 28, 1st paragraph, right column). McDonald et al. also teaches that the subject has damaged tissue in the intestinal mucosa and liver, in the language of claims 3, 4, and 6 (p. 32, table 4). McDonald et. al. also teaches the effective amount of beclomethasone dipropionate to be administered as 8 mg per day (p. 29, left column, under the heading *Formulation of BDP and Placebo Capsules*), within the range of 4-12 mg/day set by the instant claim 2. McDonald et. al. also discloses that the capsules administered were either uncoated (to dissolve in the stomach) or enteric-coated (to dissolve in the

intestine) in the language of instant claim 10(p. 29, left column, under the heading *Formulation of BDP and Placebo Capsules*). McDonald discloses that the treatment was well-tolerated, and that typical side effects of corticosteroids, such as microbial infections, hypercortisolism, and adrenal insufficiency, were not observed during the treatment. (p. 32, left column, first paragraph, under the heading, "Toxicity from Treatment," and p. 33, left column, last paragraph – right column, first paragraph) McDonald et. al. also reveal the aim for the study therein to compare the effectiveness of oral BDP to that of placebo capsules in the claimed method herein, and also to examine the frequency of infection in patients treated with beclomethasone dipropionate. See abstract and the entire article, especially p. 29, left column, first paragraph and right column, 3rd paragraph. McDonald et al. does not expressly disclose the long-term therapy (i.e., 29-56 days) in the claimed method, or therapy wherein administration of the topically active corticosteroid commences at least 29 days post-transplantation.

Bertz et al. discloses a method of treating graft-versus-host disease by administering oral budesonide as a topically active corticosteroid. (p. 1186, left column, second paragraph - right column, third paragraph) At enrollment, patients had a mean time of 30 days since transplantation, with actual times ranging between 10 and 310 days. (p. 1186, left column table 1) The duration of the therapy was between 6-70 days, varying from patient to patient, with no side effects observed in any patient. (p. 1187, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to orally administer BDP alone or with prednisone over the long term (i.e. 29-56 days) starting at least 29 days post-transplantation. One having ordinary skill in the art at the time of the invention would have been motivated to orally administer BDP alone or with prednisone in the long term (i.e. 29-56 days) since the administration of BDP alone or with prednisone for 30 days or les is known according to the prior art, and a subject may not have fully recovered from their condition after 30 days, and further because Bertz et al. discloses that budesonide, which is a similar topically active corticosteroid, can also be administered for the treatment of graft-versus-host disease. Thus, one of ordinary skill in the art would reasonably extend the therapy to the longer period from 30 days or less to 56 days if such treatment is still required after 30 days from the beginning of treatment. One of ordinary skill in the art would reasonably have expected success in administering the therapy for more than 30 days because McDonald discloses that no side effects were noticed in patients administered beclomethasone dipropionate, and furthermore because Bertz et al. discloses that patients maintained on a similar topically active corticosteroid, budesonide, showed no side effects when maintained on the drug for up to 70 days. In view of these disclosures, one of ordinary skill in the art would have determined that beclomethasone dipropionate could reasonably be administered for a duration of over 30 days due to the observed lack of side effects for topically active corticosteroids. Moreover, determination of the time period of administration is considered well within the skill of the artisan, involving merely routine skill in the art.

Furthermore, it would have been obvious to begin the therapy at least 29 days post-transplantation (for example in patients who are discontinuing prednisone therapy) because many of the patients studied by Bertz et al. are begun on topically active corticosteroid therapy at more than 29 days, in some cases as long as 310 days after transplantation. One of ordinary skill in the art would reasonably have interpreted these results to indicate that patients 29 or more days post-transplantation can be started on topically active corticosteroid therapy with a reasonably expectation of success.

Thus the invention as a whole is *prima facie* obvious over the prior art.

Response to Argument: Applicant's arguments and amendment submitted May 29, 2008 as applied to the above rejection have been fully considered and not been found persuasive to remove the above rejection.

Applicant argues that the declaration of McDonald, of record in a previous office action, is persuasive to overcome the above rejection. In particular, Applicant argues that the McDonald declaration demonstrates that at the time of the invention one of ordinary skill in the art would not have been able to perform the claimed method for fear that the patient would suffer intolerable side effects. This statement is overcome by the fact that neither McDonald et al. nor Bertz et al. discloses intolerable side effects, or any side effects for that matter. Although clearly one of ordinary skill in the art would have remained vigilant against the possibility of side effects, monitoring a patient to make sure that a particular therapy is well tolerated is part of the ordinary and routine level of skill in the art, and one of ordinary skill in the art would not have faced any undue burden in cautiously extending the therapy in cases where the benefit outweighs the

risks. Even if some side effects occur, they must be weighed against the consequences of stopping therapy. Otherwise how is any new therapeutic method ever shown to be safe? The fact that the declarant discontinued therapy is not persuasive to show that continuation of therapy would necessarily be beyond the ordinary skill in the art, as the declarant was not aiming to find the longest therapeutically acceptable course of therapy. This is especially true in view of the teaching of Bertz et al. that a similar topically active corticosteroid, budesonide, did not produce side effects in longer courses of therapy. In other words, the declarant has not shown that there would be any difficulties in extending the therapy that could not be met by one of ordinary skill in the art.

Applicant further argues that Bertz et al. is disqualified as a reference due to the fact that the claims now claim only methods using beclomethasone dipropionate and no longer encompass budesonide. However, one of ordinary skill in the art would have recognized that both beclomethasone dipropionate and budesonide are described in the references as being topically active corticosteroids. Thus they would be expected to have similar effects when administered to a patient. Therefore the fact that Bertz et al. managed to administer a topically active corticosteroid over the long term without unacceptable side effects serves to validate this therapeutic approach, providing further impetus to one of ordinary skill in the art to use a similar administration schedule with BDP.

For these reasons the rejection is deemed proper and maintained.

Claims 1-10 and 12-16 are rejected under 35 USC 103(a) as being unpatentable over Baehr et. al. (Reference of record in previous office action) in view of Bertz et al. (Reference of record in previous action)

Baehr et. al. teaches that oral administration of the particular topically active corticosteroid, beclomethasone dipropionate, alone in the form of a capsule for 28 days, is a useful method of treating graft-versus-host disease in a human following organ allograft transplantation of human leukocyte antigen mismatched marrow. (p. 1233, right column, under the heading, *clinical efficacy*) Patients entered the study at a mean period of 58 days post-transplantation. (p. 1233, left column, last paragraph) Baehr et. al. also teaches that, in subjects already taking prednisone, "The prednisone dose at study entry was maintained throughout the study whenever medically possible," (p. 1232. left column, 3rd paragraph) meaning that BDP was administered in conjunction with another prophylactic agent as taught by instant claim 16. Baehr et. al. also teach the use of BDP in subjects who have tissue damage of the intestinal mucosa and liver. Baehr et. al. also teaches the effective amount of beclomethasone dipropionate to be 8 capsules of 1 mg each per day, for a total dose of 8 mg per day, in accordance with instant claim 2. (p. 1232, under the heading, *formulation and dosing of beclomethasone dipropionate*) Although adrenal axis function was reduced in patents receiving BDP, no clinical side effects were observed. (p. 1234, right column, p. 1236, right column, second paragraph) Baehr et. al. also suggest that the purpose of the study is to evaluate whether the oral BDP is a safe effective treatment for the instant disease. See

the abstract of Baehr et. al. Baehr et. al. does not explicitly disclose the long-term therapy (i.e. 29-56 days) of the claimed invention.

Bertz et al. discloses a method of treating graft-versus-host disease by administering oral budesonide as a topically active corticosteroid. (p. 1186, left column, second paragraph - right column, third paragraph) At enrollment, patients had a mean time of 30 days since transplantation, with actual times ranging between 10 and 310 days. (p. 1186, left column table 1) The duration of the therapy was between 6-70 days, varying from patient to patient, with no side effects observed in any patient. (p. 1187, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to orally administer BDP alone or with prednisone over the long term (i.e. 29-56 days), beginning at least 29 days after transplantation.

One having ordinary skill in the art at the time of the invention would have been motivated to orally administer BDP alone or with prednisone in the long term (i.e. 29-56 days) since the administration of BDP alone or with prednisone for 30 days or les is known according to the prior art, and a subject may not have fully recovered from their condition after 30 days, and further because Bertz et al. discloses that budesonide, which is another topically active corticosteroid having similar biological effects, can also be administered for the treatment of graft-versus-host disease. Thus, one of ordinary skill in the art would reasonably extend the therapy to the longer period from 30 days or less to 56 days if such treatment is still required after 30 days from the beginning of treatment. Furthermore because Bertz et al. discloses that patients maintained on a

similar topically active corticosteroid, budesonide, showed no side effects when maintained on the drug for up to 70 days. In view of these disclosures, one of ordinary skill in the art would have determined that beclomethasone dipropionate or budesonide could reasonably be administered for a duration of over 30 days due to the observed lack of side effects for topically active corticosteroids. Moreover, determination of the time period of administration is considered well within the skill of the artisan, involving merely routine skill in the art.

Thus the invention as a whole is *prima facie* obvious over the prior art.

Response to Argument: Applicant's arguments and amendment submitted May 29, 2008 as applied to the above rejection have been fully considered and not been found persuasive to remove the above rejection.

Applicant argues that the declaration of McDonald, of record in a previous office action, is persuasive to overcome the above rejection. In particular, Applicant argues that the McDonald declaration demonstrates that at the time of the invention one of ordinary skill in the art would not have been able to perform the claimed method for fear that the patient would suffer intolerable side effects. This statement is overcome by the fact that neither Baehr et al. nor Bertz et al. discloses intolerable side effects, or any side effects for that matter. Although clearly one of ordinary skill in the art would have remained vigilant against the possibility of side effects, monitoring a patient to make sure that a particular therapy is well tolerated is part of the ordinary and routine level of skill in the art, and one of ordinary skill in the art would not have faced any undue burden in cautiously extending the therapy in cases where the benefit outweighs the

risks. Even if some side effects occur, they must be weighed against the consequences of stopping therapy in a patient who would be prone to serious autoimmune disease if untreated. Otherwise how is any new therapeutic method ever shown to be safe? The fact that the declarant discontinued therapy is not persuasive to show that continuation of therapy would necessarily be beyond the ordinary skill in the art, as the declarant was not aiming to find the longest therapeutically acceptable course of treatment. This is especially true in view of the teaching of Bertz et al. that a similar topically active corticosteroid, budesonide, did not produce side effects in longer courses of therapy. In other words, the declarant has not shown that there would be any difficulties in extending the therapy that could not be met by one of ordinary skill in the art.

Applicant further argues that Bertz et al. is disqualified as a reference due to the fact that the claims now claim only methods using beclomethasone dipropionate and no longer encompass budesonide. However, one of ordinary skill in the art would have recognized that both beclomethasone dipropionate and budesonide are described in the references as being topically active corticosteroids. Thus they would be expected to have similar effects when administered to a patient. Therefore the fact that Bertz et al. managed to administer a topically active corticosteroid over the long term without unacceptable side effects serves to validate this therapeutic approach, providing further impetus to one of ordinary skill in the art to use a similar administration schedule with BDP.

For these reasons the rejection is deemed proper and maintained.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over McDonald et. al. (References of record in previous office action) or alternately Baehr et. al. (References of record in previous office action), in view of Bertz et al. (Reference included with PTO-892) in view of, alternately, US patents Lundquist, Brancq et. al., or Benita et. al. (US patents 5843465, 5958431, and 6007826, References of record in previous office action).

The disclosures of McDonald et. al. and Baehr et. al. in view of Bertz et al. is discussed above. The above references do not disclose a method in which the active agent is administered as a pharmaceutical emulsion.

Lundquist, Brancq et. al., and Benita et. al. all disclose pharmaceutical emulsions, and methods for preparing the same from hydrophobic pharmaceutical compounds. (see, for example, claim 1 of Lundquist, claim 1 of Brancq et. al., or claim 1 of Benita et. al.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to orally administer BDP alone or with prednisone as an emulsion, in the manner of claim 11, as disclosed by the aforementioned US patents.

One having ordinary skill in the art at the time of the invention would have been motivated to administer the compound as an emulsion to increase solubility and bioavailability. One of ordinary skill in the art would have reasonably expected success because determination of the optimal dosage formulation is considered well within the skill of the artisan, involving merely routine skill in the art.

Thus the invention as a whole is *prima facie* obvious over the prior art.

Response to Argument:

Applicant's arguments and declaration submitted May 29, 2008 as applied to the above rejection have been fully considered and not been found persuasive to remove the above rejection. The reasons are the same as those discussed above concerning McDonald et al. and Baehr et al. Thus Applicant's arguments are not found to be convincing and the rejection is maintained.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/
Examiner, Art Unit 1623
8/11/2008

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner, Art Unit 1623